Neonatal Therapeutic Hypothermia

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Definition of Perinatal Asphyxia

*No agreed universal definition

**ACOG/AAP**

“Marked impairment of gaseous exchange in the fetus leading to progressive hypoxemia, hypercapnia and significant metabolic acidosis if prolonged”

They proposed the following criteria for diagnosis: umbilical cord arterial pH <7; Apgar score of 0-3 for longer than 5 min; neurological manifestations (e.g., seizures, coma, or hypotonia); and multisystem organ dysfunction, mainly cardiovascular, gastrointestinal, hematological, pulmonary or renal system dysfunction

**WHO**

“Failure to initiate and sustain breathing at birth”
Definition of Hypoxic Ischemic Encephalopathy (HIE)

*Abnormal state of neurobehavior comprising altered level of consciousness, abnormal brainstem and motor function as a result of prolonged hypoxemia and ischemia*
# Severity of HIE

Sarnat Chart for the Staging of Severity of HIE (Sarnat H.B., Sarnat M.S. 1976)

<table>
<thead>
<tr>
<th>Severity</th>
<th>Stage 1 (Mild)</th>
<th>Stage 2 (Moderate)</th>
<th>Stage 3 (Severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level of consciousness</strong></td>
<td>Hyperalert</td>
<td>Lethargic or Obtunded</td>
<td>Stupor or coma</td>
</tr>
<tr>
<td><strong>Activity</strong></td>
<td>Normal</td>
<td>Decreased</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Neuromuscular Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle Tone</td>
<td>Normal</td>
<td>Mild hypotonia</td>
<td>Flaccid</td>
</tr>
<tr>
<td>Posture</td>
<td>Mild distal flexion</td>
<td>Strong distal flexion</td>
<td>Intermittent decerebration</td>
</tr>
<tr>
<td>Stretch Reflexes</td>
<td>Overactive</td>
<td>Overactive</td>
<td>Decreased or absent</td>
</tr>
<tr>
<td><strong>Complex or primitive reflexes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suck</td>
<td>Weak</td>
<td>Weak or absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Moro (Startle)</td>
<td>Strong</td>
<td>Weak</td>
<td>Absent</td>
</tr>
<tr>
<td>Tonic neck</td>
<td>Slight</td>
<td>Strong</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Autonomic Function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupils</td>
<td>Mydriasis</td>
<td>Miosis</td>
<td>Variable</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>Tachycardia</td>
<td>Bradycardia</td>
<td>Variable</td>
</tr>
<tr>
<td>Seizures</td>
<td>None</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Category</th>
<th>Moderate Encephalopathy</th>
<th>Severe Encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consciousness</td>
<td>Lethargic</td>
<td>Stupor or coma</td>
</tr>
<tr>
<td>Spontaneous activity</td>
<td>Decreased activity</td>
<td>No activity</td>
</tr>
<tr>
<td>Posture</td>
<td>Distal flexion, complete extension</td>
<td>Decerebrate</td>
</tr>
<tr>
<td>Tone</td>
<td>Hypotonia (focal or general)</td>
<td>Flaccid</td>
</tr>
<tr>
<td>Primitive reflexes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suck</td>
<td>Weak</td>
<td>Absent</td>
</tr>
<tr>
<td>Moro</td>
<td>Incomplete</td>
<td>Absent</td>
</tr>
<tr>
<td>Autonomic system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupils</td>
<td>Constricted</td>
<td>Deviated, dilated, or nonreactive to light</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Bradycardia</td>
<td>Variable</td>
</tr>
<tr>
<td>Respiration</td>
<td>Periodic breathing</td>
<td>Apnea</td>
</tr>
</tbody>
</table>
Epidemiology of Perinatal Asphyxia

- WHO: 4 - 9 million newborn babies develop birth asphyxia annually globally

- Birth asphyxia
  - account for 23% of neonatal deaths worldwide
  - 3rd largest cause of under 5 mortality

<table>
<thead>
<tr>
<th>Location</th>
<th>Incidence/1000 live births</th>
<th>Moderate or Severe HIE</th>
<th>Case Fatality Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed Countries</td>
<td>3 - 5</td>
<td>0.5 - 1</td>
<td>0.1</td>
</tr>
<tr>
<td>Cape Town</td>
<td>4.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nigeria</td>
<td>26</td>
<td></td>
<td>≥ 40</td>
</tr>
</tbody>
</table>
Pathophysiology And Pathogenesis of HIE
Management of HIE

The understanding of the pathophysiologic and pathogenetic processes operating in asphyxia has opened new horizons to therapeutic interventions.

**General Principles**

- Prevention of intrauterine and perinatal asphyxia through fetal monitoring and safe delivery
- Supportive strategies
  - Adequate initial resuscitation
  - Respiratory and cardiovascular support
  - Nutritional and metabolic support
  - Prevention and management of multiorgan dysfunction and complications
Promoting existing endogenous neuroprotection

- Therapeutic Hypothermia*
- Erythropoietin (EPO)
- Melatonin
- Remote Ischemic Postconditioning (RIPostC)
Other Experimental Neuro-protective Compounds

- Xenon
- Magnesium sulphate
- Allopurinol
- Topiramate
- N-acetylcystine stem (NAC)
- Opioids
- Stem cell therapy
Therapeutic Hypothermia
Historical Background

- 1959: Westin’s report of favorable outcome of 6 newborn babies submerged in cold water for 20 minutes
- 1987: Busto et al report of neuroprotection in adult rats when brain temperature was lowered by only a few degrees during ischemia
- Clinical studies on cooling the newborn baby’s brain post asphyxia started around 1994
- 2005: first large RCT established the efficacy of TH in asphyxiated newborn babies (Gluckman et al Lancet 2005;365(9460):663)
Mechanisms of Action

- **Reduction of cerebral metabolism:** inhibits post depolarization release of many toxins including EAA, NO, free radicals

- **Attenuation of excitatory brain injury:** Suppresses hyperexcitability of glutamate receptors, antagonizes NMDA

- **Alleviates oxidative cascade:** TH lowers oxidative stress markers

- ** Suppresses inflammation:** TH markedly reduces cascade proteins

- **Suppresses programmed cell death/apoptosis**

- **Expands therapeutic window**
Prerequisite for TH

- Gestation ≥ 36 weeks
- Apgar score of ≤5 and need for resuscitation beyond 10 minutes after birth
- Acidosis with cord arterial blood pH of < 7.0 in the first hour of life (where available)
- Neurological signs - hypotonia, hypertonia, weak/absent suck, seizures
- Age ≤ 6 hours from birth
- Abnormal aEEG pattern (where available)
- Sarnat staging of moderate or severe asphyxia
- Ability to provide adequate supportive care and monitoring
- Absence of major congenital abnormalities
Who Benefits Most From TH?

- Babies with moderate encephalopathy and without early onset seizures have the most promising outcome.

- Babies with severe encephalopathy and/or early onset seizures have mainly necrosis as opposed to apoptosis as the general brain injury pattern hence reduced benefit.

- Severe septicemia reduces the benefit from TH.
Modalities Used for TH
1. Cool Cap
2. Tecotherm™
3. Phase Changing Materials (PCM)

- made of salt hydrides, fatty acid and esters or paraffin melting at set point
- Absorb and release heat at a nearly constant temperature
- Can store 5 - 14 times more heat per unit volume than water or masonry
The MiraCradle™
4. Others


- Ice packs: wide temperature fluctuations


Principle of TH

- Achieve rectal temperature of 33°C - 34.5°C within 3 to 4 hours
- Maintain rectal temperature steadily between 33°C and 34.5°C for 72 hours
- Rewarm the baby at a steady rate of 0.5°C per hour until a rectal temperature of 37±0.5°C is attained
- Monitor the baby closely until 80 hours
- Maintain adequate supportive care and close monitoring throughout the TH and continue intensive care after the TH
Studies Reporting Favorable Outcome In Babies Treated With TH

- Whole body cooling
  - 6 RCTs 2002 - 2011
  - 3 of these (NICHD 2005, TOBY 2009, ICE 2011) were multicenter with >100 babies per arm

- Selective head cooling
  - 6 RCTs 1998 - 2010
  - 2 of these (CoolCap 2005, Zhou 2010) were multicenter with >100 babies per arm

- Meta analysis
  - 3 Meta analysis reports 2010 - 2012
  - Each of these analyzed at least 6 studies
Efficacy of TH

TH has been shown in various studies to reduce composite outcome of:

- Death or major neurodevelopmental disability
- Mortality
- Major disability at the age of 18 months
- Cerebral palsy
- Developmental delay
- Blindness
Adverse Effects of TH

- Sinus bradycardia
- Thrombocytopenia
- Background abnormal aEEG/Seizures
- Increased multiorgan injury
Conclusion

- Perinatal asphyxia remains a major cause of neonatal mortality and burden of disease in emerging economies.
- Better understanding of the pathogenesis in asphyxia has opened for clinical trials of possible future interventions.
- Therapeutic Hypothermia offers the most promising neuroprotective intervention in moderate and severe perinatal asphyxia at the present time.
- There is an urgent need to develop more of the cheaper, effective and easier to apply modalities for TH.
- Gaps in knowledge and gray areas still exist with regard to application and actions of TH, especially its use in late preterm babies.